administering a reference substance to a gene-mutated animal according to claim 1, then determining a total amount of amyloid β in the brain (N) and the amount of amyloid β 40 and amyloid β 42 in the brain, then calculating a ratio of amyloid β 42/amyloid β 40 (Q); and

comparing the value of M to N, or the value of P to Q.

Please add new claim 51 as follows:

--- 51. A non-human gene-mutated animal having a mutant presenilin-1 gene which encodes for the OS-2 type mutation of presenilin-1. ---

REMARKS

Initially, Applicants thank the Examiner for returning a duly initialed copy of the Form PTO-1449 with the Office Action, indicating consideration of the Information Disclosure Statements filed August 22, 2002, and December 18, 2000.

Reconsideration and withdrawal of the rejections of record in view of the foregoing amendment and the following remarks is respectfully requested.

Summary of Status of Amendments and Office Action

In the present amendment, claims 1, 3-6, 12, 13, 16 and 36 are amended, and claim 51 is added. Therefore, claims 1-51 are pending with claims 1, 3-6, 10, 18-22, 24, 25, 27, 29, 34, 43 and 51 being independent.

In the Office Action, the Restriction Requirement of July 22, 2002 is deemed proper and made final.

In the Office Action, claims 1-2, 5-9, 12-17, 33 and 36-42 are rejected and claims 3-4,10-11, 18-32, 34-35 and 43-50 were removed from consideration.

Claims 1, 2, 5-9, 12-17, 33 and 36-42 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 5-9, 12-17, 33 and 36-42 are rejected under 35 U.S.C. § 112, first paragraph as nonenabled.

Claims 1, 2, 5-9, 12-17, 33 and 36-42 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

Claims 1, 2, 33 and 36-42 are rejected under 35 U.S.C. § 102(e) as anticipated by Zheng et al (Pub No. US 2002/0016978) and George-Hyslop et al (US Patent No. 6,395,690).

Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as anticipated by Duff et al.

Claims 5-7, 12-17, 22 and 36-42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kamino et al in view of Duff et al. or George-Hyslop et al.

Explanation and Support for Amendments

Applicant submits that each of the foregoing amendments is fully supported by the specification at pages 3-6.

Response to Restriction Requirement

Applicants note that the Examiner has made the Restriction Requirement final. However, Applicants again submit that the restriction requirement is in error and should be withdrawn. Specifically, Applicants note that there is a significant amount of overlap in the Groups set forth by the Examiner. There should be no undue burden for the Examiner to examine each of the groups of invention. Therefore, the restriction should be withdrawn.

Response to §112, First Paragraph Rejection

Claims 1, 2, 5-9, 12-17, 33 and 36-42 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection asserts that the claimed invention encompasses transgenic animals as well as knockout animals or non transgenic animals, and there is no description of the phenotype of any of these animals. The rejection asserts that the phenotype of transgenic or knockout animals is highly unpredictable and a representative number of species have not been sufficiently described by other relevant identifying characteristics.

In response, Applicants note that the claims now explicitly state that the gene-mutated animal is created using a knockin methodology, and not knock out. Support for this recitation is found throughout the specification, and particularly at page 5 which discusses the advantages of using a knockin animal versus using a knock out animal.

Further, as the specification sets forth at page 17, knockin animals are generally created using embryonic stem (ES) cells. The cells are transformed with a vector which replaces the naturally occurring PS-1 gene with that encoded in the vector by homologous recombination. Thus, the identity of the mutations is known prior to insertion in the chromosome (*i.e.*, the genotype). The transformed ES cells are then "sprinkled" onto 8-cell mouse embryos, which are then reinserted into pseudo-pregnant mice to produce chimeric offspring having the mutant PS-1 gene. Using standard everyday techniques, these chimeric mice can then be mated with other mice, ultimately giving homozygous mutant PS-1 mice. At this stage, the phenotype is identified. The rejections assertion that the specification does not identify the phenotype is, therefore, misplaced and should be withdrawn. The specification describe the invention in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, a knockin non-human gene-mutated animal having a mutant presenilin-1 gene.

Claims 1, 2, 5-9, 12-17, 33 and 36-42 are also rejected under 35 U.S.C. § 112, first paragraph as nonenabled. The rejection acknowledges that the specification is enabling for a knockout transgenic mouse whose endogenous presenilin-1 gene has been mutated by homologous recombination, a cell isolated from the transgenic mouse and a method of using the transgenic mouse for evaluating therapeutic compounds that may be useful in treating or preventing Alzheimer's disease. The rejection asserts that the specification does not provide any guidance as to how to produce transgenic animals other than mice and that the art of creating transgenic animals is

unpredictable, and therefore, the specification does not provide enough guidance to produce non-mouse transgene animals which fall within the scope of the claim.

Applicants respectfully submit that an applicant for a patent is not required to exemplify each and every limitation of the claims. See In re Borkowski and Van Venrooy, 164 USPQ 642, 646 (CCPA 1970) "[m]oreover, there is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'" Applicants specification adequately discloses a method to enable one of ordinary skill in the art to create additional knockin non-human gene-mutated animals from those disclosed in the specification. Applicants respectfully submit that in light of the amendment of independent claims 1 and 3-6 to knockin animals and in light of the discussions above, the rejection is moot and should be withdrawn.

For these reasons, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 2, 5-9, 12-17, 33 and 36-42 are rejected under 35 U.S.C. § 112, first paragraph.

Response to §112, Second Paragraph Rejection

Claims 1, 2, 5-9, 12-17, 33 and 36-42 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The rejection asserts that Claim 1 is indefinite because it is unclear whether the claimed animal has one mutant gene, or more than one mutated gene. The rejection also asserts that claims 5-9 are indefinite because it is unclear which of SEQ ID Nos. 1-4 are wild type, and which are mutant. The rejection also asserts that claim 12, 16 and 17 is indefinite because there is insufficient antecedent basis for the limitations "amyloid beta protein" and "the mutant presenilin-2

gene." The rejection also asserts that claim 13 is indefinite because there is insufficient antecedent basis for the limitations "the mutant presenilin protein" and "the mammal." Finally, the rejection asserts that claim 36 is vague and indefinite because it is unclear as to what the steps of the method are, and the step given is confusing.

In response, Applicants note that claim one has been amended to recite a "knockin non-human gene-mutated" animal. Knockin animals are created by replacing the naturally occurring gene with a new gene. Therefore, one of ordinary skill in the art would understand that the animal has at least one mutant gene, but may have as many mutant genes as the animal has presenilin-1 genes encoded in its chromosome, usually two. With respect to the rejection of claims 5-9, the specification at line 4, page 13 states that SEQ ID Nos. 1-4 are examples of DNA encoding wild type presenilin-1 proteins.

With respect to the rejection of claims 12, 16 and 17, Applicants have removed reference to presenilin-2 (without disclaimer thereof) from the claims. With respect to the rejection for lack of antecedent basis for the term "amyloid β," Applicants have rewritten the claim to better point out that the overexpression of amyloid β is a result of the mutation in the presenilin-1 gene of the gene-mutated animal. There is no need to provide basis for the term "amyloid β" before this claim because it is a further result of the mutated presenilin-1 gene and would not be the end result of all mutations in the presenilin-1 gene. The claims as written do not lack antecedent basis, and are fully supported by the specification.

With respect to the rejection of claims 13 and 36, claim 13 has been rewritten to eliminate the lack of antecedent basis, and claim 36 has been rewritten to state the steps in the claimed method. Claim 36 as rewritten is supported by pages 1-4 of the specification.

For these reasons, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 2, 5-9, 12-17, 33 and 36-42 under 35 U.S.C. § 112, second paragraph.

Response to §§102 and 103 Rejections

Claims 1, 2, 33 and 36-42 are rejected under 35 U.S.C. § 102(e) as anticipated by Zheng et al (Pub No. US 2002/0016978) and George-Hyslop et al (US Patent No. 6,395,690). Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as anticipated by Duff et al. The rejection asserts that these references teach transgenic mice having presenilin-1 genes, and Duff further teaches a transgenic mouse which expresses a mutant presenilin-1.

In response, Applicants note that these references do not teach the creation of knockin animals having mutant presenilin-1 genes, and therefore, cannot anticipate the claims. Further, with respect to newly added claim 51, these references do not disclose gene-mutated animals having the OS-2 mutation of presenilin-1 inserted, and therefore, do not anticipate this claim.

Claims 5-7, 12-17, 22 and 36-42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kamino et al in view of Duff et al. or George-Hyslop et al. The Examiner asserts that Kamino teaches mutations which are present in early onset Alzheimer's, Duff teaches a transgenic mouse which expresses a mutant presenilin-1, and also discloses the increase of beta amyloid in these mice, which correlates to the pathogenic route followed by Alzheimer's disease. The Examiner finally

asserts that George-Hyslop teaches a transgenic mouse expressing human presenilin-1. The Examiner asserts that it would be obvious to modify the vectors of Duff or George-Hyslop using the mutations of Kamino to produce a transgenic mouse with a reasonable expectation of success and use the mouse in methods of evaluating therapeutic or preventive compounds usable in Alzheimer's disease treatment.

In response, Applicants note that the combination of Kamino and Duff or Kamino and George-Hyslop or Kamino, Duff and George-Hyslop (even assuming the combination is proper)would not result in Applicants' invention because they do not teach, suggest or otherwise motivate one to create a knockin gene-mutated animal having a mutant presenilin-1 gene. Further, as noted at page 4 of the specification, Applicants have discovered that the creation of knockin animals has overcome many of the problems inherent with other methods of creating transgenic animals having mutant presenilin-1 genes. The combination of these documents does not lead to Applicants claimed invention, nor does it suggest or motivate one of ordinary skill in the art to create Applicants invention.

For these reasons, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 2, 5-7, 12-17, 22, 33 and 36-42 under 35 U.S.C. §§ 102 and 103.

CONCLUSION

Applicants submit that the foregoing arguments traverse the Examiner's objections and rejections.

Allowance of the application with an early mailing date of the Notices of Allowance and Allowability is therefore respectfully requested. For the reasons advanced above

Should there be any questions, the Examiner is invited to contact the undersigned at the below listed telephone number.

Respectfully Submitted,
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APPENDIX

MARKED-UP COPY OF AMENDED CLAIMS

1. (Amended) A knockin non-human gene-mutated animal having a mutant presenilin-1 gene.

3. (Amended) A knockin non-human gene-mutated animal having a mutant presenilin-1 gene which comprises a DNA having a sequence encoding a mutant presenilin-1 protein which has an amino acid sequence in which one or more amino acids at positions selected from the group consisting of amino acids numbers 79, 82, 96, 115, 120, 135, 139, 143, 146, 163, 209, 213, 231, 235, 246, 250, 260, 263, 264, 267, 269, 280, 285, 286, 290, 318, 384, 392, 410, 426 and 436 is substituted with different amino acids in the amino acid sequences of presenilin-1 protein.

4. (Amended) A knockin non-human gene-mutated animal having a mutant presenilin-1 gene which comprises a DNA having a sequence encoding a mutant presenilin-1 protein which has one or more mutations selected from the group consisting of A79V, V82L, V96F, Y115H, Y115C, E120K, E120D, N135D, M139V, M139T, M139I, I143F, I143T, M146L, M146V, H163Y, H163R G209V, I213T, A231T, A231V, L235P, A246E, L250S, A260V, C263R, P264L, P267S, R269G,[R269G,] R269H, E280A, A285V, L286V, S290C, E318G, G384A, L392V, C410Y, A426P and P436S in the amino acid sequences of presenilin-1 protein, wherein each alphabet represents an amino acid expressed as a one-letter symbol, each number represents an amino acid number from the n-terminus of the presenilin-1 protein, and the descriptions means that a wild-type amino acid shown in the left of the [numerical figure] number is substituted with an amino acid shown [in] on the right.

5. (Amended) A knockin non-human gene-mutated animal having a mutant presenilin-1 gene which comprises a DNA having a sequence encoding a mutant presenilin-1 protein in which isoleucine at position 213 of a presenilin-1 protein is substituted with an amino acid other than isoleucine.

6. (Amended) A knockin non-human gene-mutated animal having a mutant presenilin-1 gene which comprises a DNA having a sequence encoding a mutant presenilin-1 protein in which isoleucine at position 213 of a presenilin-1 protein is substituted with threonine.

12. (Twice Amended) The gene-mutated animal according to claim 1, wherein the mutant presenilin-1 results in overexpression of amyloid β protein [is caused by the mutant presenilin-1 gene and/or the mutant presenilin-2 gene].

13. (Twice Amended) The non-human gene-mutated animal according to claim 1, wherein the animal can express a mutant presenilin-1 protein and wherein the expression of said protein induces the production of amyloid β protein in an amount sufficient to form a progressive neural disease in a peripheral portion of the cerebral cortex of the brain of the [mammal] animal.

16. (Twice Amended) The non-human gene-mutated animal according to claim 1, wherein the [aforementioned] presenilin-1 gene [and/or the aforementioned presenilin-2 gene are] is transferred by homologous recombination.

36. (Twice Amended) A method for evaluating [a substance useful for] the therapeutic effect [and/or] or preventive treatment of a test substance on Alzheimer's disease, which comprises [the step of subjecting the gene-mutated animal according to claim 1 which is

administered with a test substance to a comparison with said gene-mutated animal not administered with the test substance]:

administering a test substance to a gene-mutated animal according to claim 1, then determining a total amount of amyloid β in the brain (M) and the amount of amyloid β 40 and amyloid β 42 in the brain, then calculating a ratio of amyloid β 42/amyloid β 40 (P);

administering a reference substance to a gene-mutated animal according to claim 1, then determining a total amount of amyloid β in the brain (N) and the amount of amyloid β 40 and amyloid β 42 in the brain, then calculating a ratio of amyloid β 42/amyloid β 40 (Q); and

comparing the value of M to N, or the value of P to Q.